IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Heidi Lopez de Diego, et al.
Application No.:	10/568,572
Filed:	August 14, 2006
Group Art Unit:	1624
Examiner:	Emily B. Bernhardt
Confirmation No.	6471
For:	SUCCINATE AND MALONATE SALT OF TRANS-4-((1R,3S)-6-CHLORO-3-PHENYLINDAN-1-YL)-1,2,2-TRIMETHYLPIPERAZINE AND THE USE AS A MEDICAMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

DECLARATION OF **RENÉ HOLM** UNDER 37 C.F.R. 1.132

I, René Holm hereby declare as follows:

1. I am a citizen of Denmark, more than twenty-one years of age.

2. I received a Master in Science (pharm) degree in 1998 and a Doctor of Philosophy (pharm) degree in 2002, both from the University of Copenhagen, and a Graduate Diploma in Business Administration in 2006 from the Copenhagen Business School.

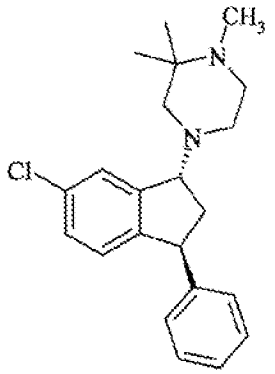
3. I have been employed at H. Lundbeck A/S, the assignee of the present application, for 9 years, holding positions of Pharmaceutical Scientist, Pharmaceutical Specialist, Head of Section, Biopharmacy, and Head of Department, Preformulation, since 2007.

4. I have been an adjunct faculty member of the Pharmaceutical Sciences department, University of Copenhagen, since 2002, where I teach graduate courses, and participate as an examiner of bachelor and master projects and the written drug formulation exam and as a member of the Scientific Appointments Committee. Since 2008, I have been an adjunct faculty member of Roskilde University as an examiner for master projects in

physical and biophysical chemistry, and of Aalborg University, where I teach Ph.D. and graduate courses in drug development and physical chemistry.

5. A short version of my curriculum vitae is attached as **Exhibit A.**

6. I have reviewed the above-identified patent application ("the '572 Application"), which discloses succinate and malonate salts of *trans*-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I):



(I),

pharmaceutical compositions and methods of treatment comprising either such salt.

7. I have reviewed, in connection with the '572 Application, the May 13, 2008 Office Action ("2008 OA"), the November 13, 2008 response to the 2008 OA, and the January 22, 2009 Final Office Action ("2009 FOA"), along with the Bøgesø references cited therein [*i.e.*, 1995 *J. Med. Chem.* article ("the Bøgesø article") and patents: EP 638 073 ("EP'073") and US 4,443,448 ("US'448")], pending claims and the amended claims being submitted with this Request for Continued Examination (RCE). The RCE claims provide that the invention includes the crystalline hydrogen succinate salt of (I), a pharmaceutical composition comprising this crystalline salt, and methods that use this crystalline salt for the treatment of a number of central nervous system diseases and disorders. I make this Declaration in support of the patentability of the RCE claims.

8. Identifying the optimum solid form of a pharmaceutical drug candidate (*i.e.*, a compound) is scientifically and clinically necessary. The compound's behavior will depend not only on its molecular structure, but also its solid form, which dictates its properties, including stability, solubility, bioavailability, among many others.

9. Solid forms of a compound can be in two states: amorphous and crystalline. Briefly, some differences between these solid states are that crystalline forms have an ordered arrangement of molecules, atoms or ions (units) that maximize the space the units occupy, whereas amorphous forms have a random orientation of the molecules, atoms or ions; and crystals have long-range order (*i.e.,* the repetition of units of the substance over long atomic distances), while amorphous solids do not, but rather have localized order proximate to their structural unit.

10. A crystalline compound can exist in a single-component or multi-component crystalline state. Only the compound comprises a single-component crystal. Another molecule with the compound comprises a multi-component crystal. Examples of multi-component crystals include salts, solvates, hydrates and co-crystals of a compound. Generally, solvates contain solvent "guest" molecules and "host" compound molecules. In hydrates, the "guest" molecules are water molecules and in co-crystals, the "guest" molecules are solid at room temperature. A crystalline salt of a compound may be a solvate or hydrate as well. With respect to crystalline compounds, a complex molecule refers to a crystalline compound existing in a multi-component crystalline state.

11. Any crystalline solid may exhibit polymorphism, *i.e.,* having more than one crystalline form.

12. Whether a compound can crystallize is unpredictable. This has long been known in the art and despite the recent progress in the art, such as in the field of crystal structure prediction (CSP), it continues to be the case with respect to complex molecules, such as pharmaceutical drug candidates.

13. For example, the state of the art at the time the invention was made provides that polymorphism of an organic molecule could not be predicted (*see e.g.,* Price, 2004), "the whole issue of CSP is full of difficulty", not just with respect to polymorphism (*see e.g.,* Desiraju, 2002), and that crystal structures of small organic molecules were occasionally predictable under reliable conditions, but with low success rates and not with one consistently successful method (*see e.g.,* University of Cambridge, 2007 (noting 1999, 2001 and 2004 prediction studies)). Moreover, the recent state of the art continues to be unpredictable despite reported "major advances" in 2007 for CSP of small organic molecules. *Id.* This small study of the predictions of seven groups was

cautiously applauded since "there [was] plenty room for improvements" including with respect to "complex compounds" such as salts and solvates, as well as polymorph stability as a function of crystallization conditions. *Id.*

14. Despite the facts that crystallizing a salt may be attempted if an ionizable group is present with an acceptable counterion and with the choice of logical combinations from which to start, presently one of ordinary skill in the art cannot know in advance whether the salt will form and cannot predict if it will be crystalline, its crystal type(s) and properties.

15. Clearly, it was not predictable at the time the invention was made that *trans*-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) would crystallize into its hydrogen succinate salt. Consequently, there was no reasonable expectation that a hydrogen succinate salt of (I) could be obtained, much less that it would be of a crystalline solid state.

16. Also, it was not predictable then, and thus unexpected, that the crystalline hydrogen succinate salt of (I) would be polymorphic. In fact, as disclosed in the application, the alpha form was obtained when repeating the acetone salt crystallization procedure that initially provided the beta form (*see e.g.,* [0123] of the published version of the '572 Application ("the published '572 Application"). It was found that the thermal characteristics: melting point (onset) and enthalpy of fusion of this initial batch of the crystalline salt was lower than that of following batches, and x-ray powder diffraction (XRPD) measurements confirmed that two polymorphic forms existed (*see e.g.,* [0022] to [0030] and Figs. 1-2, of the published '572 Application).

17. Also, there are unexpected advantages associated with the crystalline hydrogen succinate salt of (I) in comparison with the fumarate salt of (I) of the prior art. Experiments were conducted in the laboratory at H. Lundbeck A/S, Valby, Denmark, and were performed as described in the specification of the present invention (noted here with respect to the published '572 Application) or as otherwise specified here.

18. To begin with, it is surprising that the hydrogen succinate salt of (I) is more stable than the fumarate salt of (I), including under accelerated conditions (*e.g.,* 90 °C) as it showed no degradation, unlike the fumarate salt (*see e.g.,* Example 19 of the published '572 Application). This likely allows for production of dosage forms comprising (I) (*e.g.,*

tablets or capsules) that have a longer shelf-life. This improved property clearly provides practical advantages for (I) as a pharmaceutical drug candidate.

19. It also is surprising that the crystalline hydrogen succinate salt of (I) is much more soluble than the fumarate salt of (I). For instance, Example 18 of the application shows that the alpha form of the crystalline hydrogen succinate salt of (I) is about 9 times more soluble in water than the fumarate salt of (I). Because it was not possible to obtain the beta form again using the acetone procedure indicates that the beta form is a thermodynamically metastable form; and thus, it is expected to have an even higher solubility than the stable alpha form; and therefore, be even more soluble with respect to the fumarate salt of (I). This is advantageous significantly and practically since an enhanced solubility may offer improved therapeutic utility of (I). For example, solubility influences absorption of the compound in the body and bioavailability, which in turn are important for the therapeutic usefulness of a pharmaceutical drug candidate.

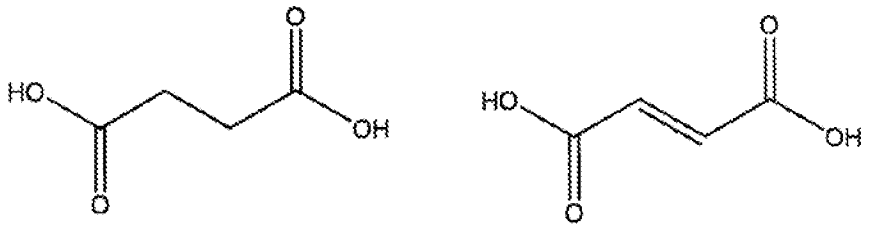
20. It is also surprising that the crystalline hydrogen succinate salt of (I) has an intrinsic dissolution rate (IDR) 20-fold greater than the fumarate salt of (I). The fumarate salt of (I), tested on 26th of September 2002, has an IDR of 0.13 mg/cm^2/min, while the crystalline hydrogen succinate salt of (I), tested on the 23th of June 2003, has an IDR of 2.66 mg/cm^2/min. Attached hereto as **Exhibit B** are the IDR results along with experimental conditions and testing dates.

21. The greater IDR of the crystalline hydrogen succinate salt of (I) is suggestive of its bioavailability, which can influence its overall therapeutic efficacy. For example, from a pharmaceutical point of view, a high IDR indicates that the particle size of a compound is less important to ensure a good dissolution profile, and hence ensure that the compound in a final dosage form is released in the small intestine where it is intended to be absorbed. Thus, the enhanced IDR may offer an improved therapeutic utility of (I) -- again, a significant and practical advantage for a pharmaceutical drug candidate.

22. These characteristics of the crystalline hydrogen succinate salt of (I) are surprising and unexpected since one of ordinary skill in the art could not predict the crystalline hydrogen succinate salt of (I), much less its characteristics, as previously mentioned. *See e.g.*, paragraphs 8-16.

23. These characteristics of the crystalline hydrogen succinate salt of (I) are also surprising and

unexpected since one of ordinary skill in the art would not have reasonably expected that a salt of an acid having a similar molecular structure to the acid of the prior art salt would have more advantageous properties. In other words, because succinic acid differs from fumaric acid by one double bond as shown here:



Succinic acid Fumaric acid

one of ordinary skill in the art would not have reasonably expected that the properties of the two salts of (I) would be significantly different, as in the about 9 times greater solubility, not to mention the 20-fold greater intrinsic dissolution rate and better stability, including under stress conditions.

24. The Bøgesø references cited by the Examiner in the 2008 OA and 2009 FOA do not teach or suggest the crystalline hydrogen succinate salt of the present invention. The 1995 Bøgesø *J. Med. Chem* article ("the Bøgesø article") discloses the fumarate salt of (I) and its racemate. It discloses that these compounds achieved the intended goal (see e.g., pp. 4381 and 4386). It does not disclose a succinate salt of (I), as acknowledged by the U.S. patent office ("the Office) (*see e.g.*, p. 6 of the May 15, 2008 Office Action ("2008 OA"). In fact, it does not disclose any other acid addition salt of (I) (*see e.g.*, Tables 3-5) or any difficulties with the fumarate salt of (I), such as difficulty in handling or preparing (see e.g., Experimental Section). Hence, it does not provide a suggestion or motivation to pursue a succinate salt of (I). It also does not provide any suggestion or motivation to one of ordinary skill in the art that a succinate salt of (I) should be made, much less that that if one was to attempt, one would have a reasonable likelihood of success or that if successful, that the succinate salt would offer improved properties, such as stability, solubility and intrinsic dissolution. Such is also certainly true of the Bøgesø article with respect to the instant crystalline hydrogen succinate salt of (I).

25. Bøgesø EP 638 073 ("EP'073") discloses generically the racemate of (I) (*see e.g.*, paragraph [0002] and p. 6 of 2008 OA). Bøgesø US 4,443,448 ("US'448) discloses 1-piperazino-3-phenyl-indane derivatives (*see e.g.*, Abstract). Both references disclose succinic acid as a possible acid addition salt (*see e.g.*, paragraph [0023] and col. 32, lines 26-43, respectively). Both references do not disclose the (1R,3S)-enantiomer (I), much less its crystalline hydrogen succinate salt and their disclosures with respect to succinic acid is no more than a general acknowledgement that other acid addition salts could be tried to achieve other salt forms of the compounds taught in each reference. However, the references do not provide any guidance as to which of these possible salts should be selected to form different salt forms of its compounds so as to reasonably achieve the different salt form. The references do state that possible salts should be non-toxic. This, however, is no guidance toward selecting a possible salt since one of ordinary skill in the art would have known that any salt selected needed to be non-toxic. Also, each of these references is silent with respect to any difficulties with the disclosed salt forms of its compounds. Each reference, therefore, fails to provide any reason to turn to a different salt form, much less a succinate form. So, each reference alone or combined with the Bøgesø reference does not provide any teaching, suggestion or motivation that would have led one of ordinary skill in the art to attempt a succinate salt of (I).

26. Furthermore, the combined references do not provide one of ordinary skill in the art a reasonable likelihood that a succinic acid salt of (I) would successfully lead to the crystalline hydrogen succinate salt of (I) and certainly not one having the improved properties of solubility, dissolution and stability like that of the present invention.

27. Additionally, although the need for identifying an optimum solid form of a compound can provide good reason for one of ordinary skill in the art to pursue more than one salt of the compound, this does not mean that one of ordinary skill in the art can predict in advance the result of such pursuit. Such pursuit does not have predictable solutions. As previously mentioned, one skilled in the art can not know if a solid state salt will form, what solid state(s) a salt form will have and if it will have advantageous properties. Just because there appears to be a finite number of salt agents to try, it does not mean there is a finite number of "identified, predictable solutions" for obtaining a salt form of (I).

Besides selecting the acid, one of ordinary skill in the art has a number of other parameters to consider when attempting a salt form of a compound (*e.g.*, acid-base ratio, solvent type, co-solvent type, pH, temperature, heating and cooling rates, evaporation rate and time, mixing rate, and vessel design). It is reasonable for one of ordinary skill in the art to begin with apparently logical combinations, such as with pharmaceutically acceptable salt agents; however, s/he also relies on chance and serendipity when achieving a crystalline salt form of a compound because of the impossibility to foretell in a reliable way the influence a particular salt agent will have on the behavior of the host compound, as previously mentioned (*see* paragraphs 12-14).

28. Also, in the pursuit of identifying an optimum solid form of a compound, it is well known: (1) that if a pharmaceutical drug candidate is a weak organic acid or weak organic base, it can exist as a salt form; (2) that different salt forms of the compound are distinct chemical entities with their own chemical, physical and biological profiles; and (3) as such, will likely offer a more optimal solid form of the compound than the free acid or free base.

29. Consequently, it is expected that the solubility of the racemic free base of (I) would be negligible as compared to the crystalline hydrogen succinate salt of (I); and in fact, it is. See **Exhibit C** for solubility results comparison. It is also quite likely would be less stable and have a lower IDR than the crystalline hydrogen succinate salt of (I). Other properties of the racemic free base also may have been optimized by the crystalline hydrogen succinate salt of (I). However, with respect to the closest prior art compound, one of ordinary skill in the art would not deem it to be the racemic free base of (I) in view of the existence of the fumarate salt of (I) since the claimed invention is a salt form of (I), not of the racemate, and salt forms are well known to often provide the optimal characteristics of a compound, as previously mentioned (*see* paragraph 29).

30. Because of the foregoing, the crystalline hydrogen succinate salt of (I) of the present invention and its aforementioned properties are surprising, unexpected and unpredictable over the prior art fumarate salt and free base of (I).

31. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like

are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Valby 16-Feb-2010
Date

Dr. René Holm

Exhibit A

SHORT CURRICULUM VITAE, RENÉ HOLM

WORKING EXPERIENCE

2007- Lundbeck	Head of Department (preformulation), Analytical Research and Development,
2008-	Aalborg University • External teacher, In PhD and graduate courses
2008-	Roskilde University • External examiner for master projects in physical and biophysical chemistry
2002-	Copenhagen University, Faculty of Pharmaceutical Sciences • External teacher, In the elective courses, PhD and master courses • External examiner, for bachelor and master projects and the written examination in drug formulation • Member of scientific appointments committee, Assessment of scientific, administrative and teaching qualification for applicants for positions as assistant or associate professors
2006-2007 Lundbeck	Head of section (Biopharmacy). Pharmaceutical Research and Development,
2005	Pharmaceutical Specialist, Pharmaceutical Research and Development, Lundbeck
2001-2005	Pharmaceutical Scientist, Pharmaceutical Research and Development, Lundbeck
1998-2001 Denmark	PhD student, University of Copenhagen, Faculty of Pharmaceutical sciences,
1998	Pharmacist, Ølgod Pharmacy

EDUCATION

2002-2006	Graduate Diploma in Business Administration, (HD), Copenhagen Business School
1998-2001	PhD (pharm), The Danish University of Pharmaceutical Sciences
1992-1998	M.Sc. (pharm), The Danish University of Pharmaceutical Sciences
1989-1992	Mathematical student, Fredericia Amtsgymnasium

SCIENTIFIC PUBLICATIONS (in peer review journals)

Larsen, M., ***Holm, R.***, Jensen, K.G. Sveigaard, C., Brodin, B. and Nielsen, C.U. (2010). 5-hydroxy-L-tryptophan alters gaboxadol pharmacokinetics in rats: Involvement of PAT1 and rOat1 in gaboxadol absorption and elimination. Eur.J.Pharm.Sci. 39, 68-75

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Østergaard, J., Jensen, H. and ***Holm, R.*** (2009). Use of correction factors in mobility shift affinity capillary electrophoresis for weak analyte – ligand interactions. J.Sep. Sci. 32, 1712-1721.

Holm, R. ✉, Shi, W., Hartvig, R.A., Askjær, S., Madsen, J.C. and Westh, P. (2009). Thermodynamics and structure of inclusion compounds of tauro- and glyco-conjugated bile salts and β-cyclodextrin. Phys. Chem. Chem. Phys. 11, 5070-5078.

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Larsen, A., ***Holm, R.***, Pedersen, M.L., and Müllertz, A. (2008). Lipid-Based Formulations for Danazol Containing a Digestible Surfactant, Labrafil M2125CS: In Vivo Bioavailability and In Vitro Lipolysis in a Dynamic Lipolysis Model. Pharm. Res. 25, 2769-2777.

Thomsen, M., Fink-Jensen, A., Woldbye, D., Wörtwein, G., Sager, T.N., ***Holm, R.***, Pepe, L.M. and Caine, S.B. (2008). Effects of acute and chronic aripiprazole treatment on choice between cocaine self-administration and food under a concurrent schedule of reinforcement in rats. Psychopharmacol. 201, 43-53.

Thybo, P., Pedersen, B,L., Hovgaard, L., ***Holm, R.***, and Müllertz, A. (2008) Characterization and Physical Stability of Spray Dried Solid Dispersions of Probucol and PVP-K30. Pharm. Dev. Tech. 13, 375-386.

Lind, M., Jacobsen, J., ***Holm, R.***, and Müllertz, A. (2008). Intestinal lymphatic transport of halofantrine in rats assessed using a chylomicron flow blocking approach: The Influence of polysorbate 60 and 80. Eur. J. Pharm. Sci. 35, 211-218.

Holm, R. ✉, Hartvig, R.A., Nicolajsen, H.V., Westh, P., and Østergaard, J. (2008). Complexation of tauro- and glyco-conjugated bile salts with γ-cyclodextrin and 2-hydroxypropyl-γ-cyclodextrin studied by affinity capillary electrophoresis. J. Incl. Phenom. Macrocycl. Chem. 61, 161-169.

Schram, L.B., Nielsen, C.J., Porsgaard, T., Nielsen, N.S., ***Holm, R.*** and Mu, H. (2007). Food matrices affect the bioavailability of (n-3) polyunsaturated fatty acids in a single meal study in humans. Food Res. Int. 40, 1062-1068.

Holm, R., Nicolajsen, H.V., Hartvig, R.A., Westh, P., and Østergaard, J. (2007). Complexation of tauro- and glyco-conjugated bile salts with three neutral β-cyclodextrins studied by affinity capillary electrophoresis. Electrophoresis 28, 3745-3752.

Lind, M., Jacobsen, J., ***Holm, R.***, and Müllertz, A. (2007). Development of simulated intestinal fluids containing nutrients as transport media in the Caco-2 cell culture model: assessment of cell viability, monolayer integrity and transport of a poorly aqueous soluble drug and a substrate of efflux mechanisms. Eur. J. Pharm. Sci. 32, 261-270.

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Karpf, D.M., ***Holm, R.***, Garafalo, C., Levy, E., Jakobsen, J., and Müllertz, A. (2006). Effect of different surfactants in biorelevant media on the secretion of a lipophilic compound in lipoproteins using the Caco-2 cell culture Influence of the Type of Surfactant and the Degree of Dispersion on the Lymphatic Transport of Halofantrine in Conscious Rats. J.Sci.Pharm. 95, 45-55.

Holm, R. ✉, Hoest, J. (2004). Successful in silico prediction of intestinal lymphatic transfer. Int. J. Pharm. 272, 189-193.

Karpf, D.M., ***Holm, R.***, Kristensen, H.G., and Müllertz, A. (2004). Influence of the Type of Surfactant and the Degree of Dispersion on the Lymphatic Transport of Halofantrine in Conscious Rats. Pharm.Res. 21(8), 1413-1418.

Holm, R., Porter, C.J.H., Edwards, G.A., Müllertz, A., Kristensen, H.G., Charman, W.N. (2003). Examination of oral absorption and lymphatic transport of halofantrine in a triple-cannulated canine model after administration in self-microemulsifying drug delivery systems (SMEDDS) containing structured. Eur.J.Pharm.Sci. 20, 91-97.

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Holm, R., Müllertz, A., Christensen, E., Høy, C.E., Kristensen, H.G. (2001). Comparison of the Lymphatic Transport of Halofantrine from 3 Different Unsaturated Triglycerids in Lymph-Cannulated Conscious Rats. Eur.J.Pharm.Sci. 14, 331-337.

+ 23 posters and abstracts presented at international scientific conferences

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Bang-Andersen, B., Faldt, A., Mørk, A., de Diego, H.L., ***Holm, R.***, Stensbøl, T.B. (2007). Application no PA2007 00427, Compounds with combined SERT, $5HT_3$ and $5\text{-}HT_{1A}$ activity.

Bang-Andersen, B., Faldt, A., Mørk, A., de Diego, H.L., ***Holm, R.***, Stensbøl, T.B. (2007). Application no PA2007 00430, Compounds with combined SERT, $5HT_3$ and $5\text{-}HT_{1A}$ activity.

Holm, R., (2002). Application no PA2002 01064, Pharmaceutical composition comprising (S)-(+)-3-[1-[2-(1-acetyl-2,3-dihydro-1H-indol-3-yl)ethyl]-1,2,3,6-tetrahydropyridin4-4-yl]-6-chloro-1H-indole.

OTHER SCIENTIFIC WORK

Scientific reviewer in the following journals: Life Science, European Journal of Pharmaceutical Sciences, Biochemical Pharmacology, International Journal of Pharmaceutics, The AAPS journal, Current Drug Delivery and Journal of Pharmacy and Pharmacology, Lipids

Co-supervising(ed) 7 PhD students (completed and enrolled), and external supervisor on 24 master students in pharmacy, physical chemistry and nanoscience

Exhibit B

Intrinsic Dissolution Rate (IDR):

Dissolution rate of a substance depends on the particle size of the substance since smaller particles provide a larger surface area from which the substance may dissolve. In order to avoid dependency of particle size, for IDR measurements, tablets of pure substance are pressed. It is anticipated that the compressed tablets have a constant surface area and that the particle size of the substance comprising the tablet is therefore of negligible importance.

Using standard dissolution apparatus (USP type II), the tablet is mounted on a paddle in the dissolution media. Samples of released substance in media are drawn at different points in time during the experiment and the concentration of released substance is analyzed by high performance liquid chromatography (HPLC). The HPLC system was from Merck-Hitachi, the column was a Columbus C8, 5μm, 4.6 × 150 mm and the column oven was set at 45 °C, with test conditions of an injection volume of 25 μl, flow rate of 1 ml/min and acetonitrile:25 mM phosphate buffer, pH 6.0 (50:50), measured at 271 nm. The released amount of substance is calculated from the measured concentrations, and a plot of released amount versus time provides the rate of intrinsic dissolution as the slope of the curve.

IDR was measured in 0.001 M HCl at 37 °C. Two tablets of each salt were measured. Results are shown in the following table.

Table 1: Intrinsic Dissolution Rate of the Fumarate and Hydrogen Succinate Salts of *trans*-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I)

Salt of (I)	IDR ($mg/cm^2/min$)	Average IDR ($mg/cm^2/min$)	Test Date
Fumarate	0.13 0.13	0.13	26th of September 2002
Succinate	2.23 3.08	2.66	23th of June 2003

Exhibit C

Aqueous solubility comparison of racemic free base of (I) and crystalline hydrogen succinate salt of (I):

Test conditions used are similar described in the instant application (*see e.g.*, paragraph [0138] of the published '572 Application).

Table 2: Aqueous Solubility of the Racemic Free Base and Hydrogen Succinate Salt of *trans*-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I)

Sample	Solubility (mg/ml)	Test Date
Free Base	0.0006	16 of February 2010
Succinate 1:1, alpha	13	1st of September 2003